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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,653	11/14/2003	Molly Accola	FORS-08453	1634

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MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,653	ACCOLA ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed August 24, 2006. Currently, claims 28-47 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group II, Claims 28-35 and newly added Claims 36-47 in the paper filed August 21, 2006 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application claims priority to several provisional applications and as a CIP of 10/371,913, filed February 21, 2003.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 28, 31-33, 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Fonknechten et al. (Hum Genet. Vol. 88, pages 508-512, 1992).

Fonknechten teaches CFTR illegitimate transcription in lymphoid cells. Fonknechten teaches obtaining patient samples (page 508, col. 2). Fonknechten teaches extraction of RNA and cDNA synthesis. Fonknechten further teaches one step PCR-cDNA amplification followed by analysis of the amplified product (limitations of Claims 33). Fonknechten teaches amplification using 15 cycles and analysis by Southern blotting (limitations of Claims 31-32). Fonknechten teaches analysis of the PCR product for detection of a plurality of CFTR alleles using gel electrophoresis to separate the mutated fragment from the normal fragment (page 509, col. 2). Fonknechten teaches analysis of lymphocytes from whole blood (limitations of claim 36).

6. Claims 28, 31-33, 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Broude et al. (PNAS, Vol. 98, No. 1, pages 206-211).

Broude teaches a method of multiplex allele-specific target amplification based on PCR suppression. Broude teaches genotyping of DNA samples from cystic fibrosis-affected individuals by using the PS based mpxPCR (page 209). Broude teaches analyzing the F508 mutations. Broude teaches the normal and mutated primers were designed to differ by one nucleotide in length and also by the 3' terminal nucleotide.

Broude teaches performing a nested PCR and used in the first step a 29-mer nested CFTR primer in combination with the 5' outmost adapter primer in a 15 cycle PCR (limitations of Claim 28, 31, 32). Broude teaches using anonymous blood donors (page 208, col. 1)(limitations of Claim 36). The products were then analyzed on a gel.

7. Claims 37-38, 43, are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber (US Pat. 5,834,181, November 10, 1998).

Shuber teaches high throughput screening method for sequences specifically the cystic fibrosis transmembrane regulator (CFTR) gene. Shuber teaches immobilizing a plurality of the nucleic acid samples on a support; providing a multiplicity of probes containing polymers; hybridizing the immobilized samples with the multiplicity of probes containing polymers at substantially the same time; identifying the hybridized probes wherein the identification of the hybridized probes identifies the nucleic acid sequence or one or more genetic alterations. Shuber teaches that the target nucleic acid sample may be amplified to facilitate detection and identification. Examples of amplification methods include PCR, LCR, LAR, OLA, ARMS. Shuber teaches the samples from patients may be obtained from any cell source including blood cells (limitations of claim 43). Shuber teaches that DNA amplifications were performed involving simultaneous multiplexes of 3 or more amplicons. The amplifications were carried out for 28 cycles (col. 14). Shuber teaches that in certain embodiments wherein the sample is not immobilized, and is reacted with the probes in solution (i.e., rather than on a support). Shuber further teaches oligonucleotide probes which are allele-specific. Shuber

teaches 105 ASO probes (see col 18-19). Thus, Shuber teaches an assay which provides CFTR target nucleic acid from samples, amplifies the nucleic acid to generate target nucleic acids and exposes the amplified target nucleic acid to at least 20 detection assays.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 28-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsu (Clinical Chemistry, Vol. 47, No. 8, 2001) in view of The Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/cftr/app) and Fors et al.

(Pharmacogenomics, Vol. 1, No. 2, pages 219-229, 2000) and Hall (PNAS, Vol. 97, No. 15, pages 8272-8277, July 2000).

Hsu teaches a method of genotyping single-nucleotide polymorphisms by the invader assay with dual-color fluorescence polarization detection. Hsu teaches the PCR-Invader assay is a robust, homogeneous assay that has been shown to be highly sensitive and specific in genotyping single-nucleotide polymorphism markers (abstract). Hsu teaches that both alleles for each SNP may be assayed in one reaction and fluorescence polarization may be used to reduce the cost of the method. Hsu teaches that PCR product was incubated with Invader oligonucleotide and two primary probes (abstract). Hsu teaches DNA samples were used. Hsu teaches how to design probes for the Invader assay. Hsu teaches PCR amplification using 35 cycles (page 1375). Hsu teaches the benefits of the PCR-Invader technology as a homogeneous assay requiring no gel electrophoresis, purification or manual data entry. The assay can be performed in a single microtiter plate with no need for transferring or separation. Hsu further teaches the technology is flexible yet robust. Hsu teaches that the use of more than two fluorophores would allow multiplex of assays in the future.

Hsu does not specifically teach amplifying nucleic acid with less than 25 cycles and using CFTR alleles for analysis.

However, the cystic fibrosis mutation databases teaches the collection of mutations in the CFTR gene. There are currently **1542** mutations listed in this CFTR mutation database.

Moreover, Fors teaches large-scale SNP scoring from unamplified genomic DNA. Fors teaches the Invader assay offers a simple diagnostic platform to detect single nucleotide changes with high specificity and sensitivity from unamplified, genomic DNA. The Invader assay uses a structure-specific 5' nuclease (or flap endonuclease) to cleave sequence-specific structures in each of two cascading reactions. The cleavage structure forms when two synthetic oligonucleotide probes hybridize in tandem to a target. Fors teaches that the signal amplification permits identification of single base changes directly from genomic DNA without prior amplification (abstract). The Invader technology is in routine use today for high-throughput SNP screening. The technology involves a simple, cascading reaction that can detect mutations and SNPs directly from unamplified genomic DNA or RNA in a homogeneous, isothermal, FRET-based format (page 222). Figure 1 illustrates the schematic of the Invader assay which contains various oligonucleotides including an oligonucleotide which comprises various 5' and 3' positions that do not hybridize to target sequences. The technology is readily adapted to different sequences since the unlabeled analyte-specific oligonucleotides used in the primary reaction; no new dye-labeled oligonucleotides are needed (page 223, col. 1). This creates a streamlined approach to creating new assays allows rapid and accurate synthesis, purification and quantification of new SNP assay sets.

Hall specifically teaches that PCR is indispensable too in molecular biology but the use of exponential target amplification creates the possibility of amplicon cross-contamination, makes quantitative analysis complicated and reduces the specificity with which small genetic variations can be detected (page 8276, col. 2).

Therefore, it would have been prima facie obvious at the time the invention was made to generate a multiplex method for Cystic Fibrosis using the PCR Invader technology of Hsu. Moreover, the ordinary artisan would have been motivated to have used 17 cycles or fewer to avoid the well known art difficulties of PCR amplification taught by Hall. The ordinary artisan would have been motivated to have applied the PCR-Invader assay to CFTR gene mutations because CFTR gene mutations are diagnostic of Cystic fibrosis which is a debilitating disease. Moreover, Hsu specifically teaches the benefits of the PCR-invader assay as allowing multiplex analysis. Thus, detecting multiple mutations simultaneously, including over 30 mutations, would have been obvious at the time the invention was made given the number or CF mutations in the CFTR gene.

Finally, although Hsu suggests the use of 35 cycles for PCR amplification, the skilled artisan, given the teachings of Hall would have appreciated that exponential amplification introduces possibilities of amplicon cross contamination. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the selection of cycling performed was other than routine, that the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. The prior art teaches the ability to perform Invader assays with no prior target amplification

(see Fors) and Hsu teaches using 35 cycles. Thus, using an intermediate number of cycles, namely 25, 20 or 17 cycles would constitute routine optimization in the art.

Conclusion

10. No claims allowable over the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
April 30, 2007